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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/094,921	06/15/98	LINDHOFER H	80309

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EXAMINER	
HOLLERAN, A	
ART UNIT	**PAPER NUMBER**
1642	17

DATE MAILED: 11/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No.	Applicant(s)	
	09/094,921	LINDHOFER ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,13-21 and 23-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 13-21 and 23-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The request filed on August 24, 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/094,921 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 12 and 22 were canceled.

Claims 1-8, 13-21 and 23-30 are pending and examined on the merits.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

4. The rejection of claims 14,17, 18 and 28-30 under 35 U.S.C. 102(b) as being anticipated by Honsik et al (U.S. Patent 4,844,893; published July 4, 1989) is withdrawn in view of the amendment.

5. The rejection of claims 1-8, 13, 15, 16, 19-21 and 23-27 under 35 U.S.C. 103(a) as being unpatentable over Volker et al (U.S.Patent 5,911,987; issued June 15, 1999; 102(e) date Feb. 21, 1997) in view of Deo et al (U.S. Patent 5,837,243; issued Nov. 17, 1998; filed June 7, 1996) is withdrawn in view of the amendment.

Claim Rejections Maintained:

6. The rejection of claims 1-8 and 13-21 and 23-30 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

Claims 1 and 27 are indefinite because of the phrase "wherein the bispecific antibodies are members selected from the group consisting of the following isotype combinations" or because of the phrase "in which said rat/mouse bispecific antibody is selected from the group consisting of the following isotype combinations". The term "bispecific antibody" is a reference to an antibody with two binding specificities, whereas the members of the Markush group are isotype combinations. Amendment of the phrase to the following would obviate this rejection: "wherein the bispecific antibodies have isotype combinations selected from the group consisting of', followed by the list, where the last member of the list is set off with the word "and".

Claim 1 is indefinite because many of the "isotype combinations" listed as members of the Markush group include recitations describing parts of an antibody molecule other than an Fc portion of an antibody.

Claim 1 is indefinite because of the term "heterologous". Is there such a thing as a non-heterologous bispecific antibody ?

Claim 1 is indefinite because it is drawn to a method for making a vaccine product, but does not include a step or a description of the product that is made.

Claim 1 is indefinite because of the expression "capable of activating the Fc receptor-positive....". As recited it appears that this phrase modifies the Fc receptor-positive cells, however, the phrase appears to be meant to modifify the bispecific antibodies.

Claim 13 is indefinite because "the antibody-tumor cell preparation containing vaccine lacks antecedent basis. This rejection would be obviated by amending the claim to read "preparing a vaccine comprising an antibody-tumor cell preparation".

Claim 14 is indefinite because it is not clear how "step c)" may be changed from what is recited in claim 1, from which claim 14 depends. An additional step should be included.

Claims 17 and 18 are indefinite because "said mononucleated peripheral cells" lacks antecedent basis.

Claims 23, 25, and 26 are indefinite because it is not clear what is encompassed by the "tumor cell preparation". Claims 23 and 26 depend from claim 1, which does not include a step or description of the product that is made.

Claim 27 is indefinite because the phrase "said rat/mouse bispecific antibody" lacks antecedent basis.

Claim 27 is indefinite because the recited isotype combinations lack antecedent basis in claim 1.

Claims 28 and 30 are indefinite because the phrase "said mononucleated peripheral blood cells" lacks antecedent basis in claim 27 or claim 1.

7. The objection to the specification is maintained. The specification is objected to because it relies on a reference to subject matter disclosed within a claim. At page 20, line 21, the specification contains a reference to claim 1. Applicant is advised to review the specification for further instances of references to claims within the disclosure of the specification.

8. The rejection of claim 23 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for the reasons of record. This rejection is also applied to claims 24 and 25.

Claims 23 and 24 are drawn to methods of prevention of tumorous diseases as well as to methods of treatment. Thus, claims 23 and 24 may be interpreted as drawn to methods for the prevention of cancer. Claim 25 may be interpreted as drawn to methods for the prevention of cancer because claim 25 is directed to a method for immunizing an individual against tumor cells. Because the methods requires the use of bispecific antibodies that bind to specific tumor antigens, and because a method of prevention implies that the cancer has not yet occurred, it is not possible to understand how applicant will know which antibodies to use. Moreover, because one of the steps of the claimed method requires the isolation of autologous tumor cells, it is not clear how one may perform the claimed method in an individual who does not yet have cancer. Thus, the specification provides no teachings that would allow one of skill in the art to understand that applicant was in possession of a method for the prevention of cancer.

9. The rejection of claim 27 under 35 U.S.C. 103(a) as being unpatentable over Volker et al (U.S.Patent 5,911,987; issued June 15, 1999; 102(e) date Feb. 21, 1997) in view of Deo et al (U.S. Patent 5,837,243; issued Nov. 17, 1998; filed June 7, 1996) and further in view of Lindhofer et al (Lindhofer, H. et al, J. Immunology, 155: 219-225, 1995) is maintained.

As noted above, the isotype combinations recited in claim 27 lack antecedent basis in claim 1. Thus, for the purposes of comparison with the prior art, claim 27 is treated as an independent claim that includes the limitations of claim 1.

Claim 27 is interpreted as drawn to methods using bispecific antibodies having a combination isotype of rat-IgG2b/mouse-IgG2a, rat-IgG2b/mouse-IgG2b or rat-IgG2b/mouse-IgG3. Neither Volker nor Deo teaches making vaccine preparations using combination isotype bispecific antibodies. However, Lindhofer teaches that rat/mouse combinations made using the quadroma technique result in a higher yield of functional bispecific antibodies and also teach that a rat/mouse combination isotype is easier to purify (see pages 219-221 and Figure 1). Thus, it would have been prima facie obvious to one of ordinary skill in the art to have combined the teachings of Volker with that of Deo and Lindhofer to have made the claimed invention. One would have been motivated to combine the teachings of Lindhofer with that of Volker and Deo, because Lindhofer teaches the advantages of using rat/mouse combinations in purification of bispecific antibodies and in generating high yields of usable antibody product.

10. The rejection of claims 1-8, 13-21, 24-26, and 28 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement commensurate with the scope of the claimed invention is maintained for the reasons of record. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation

necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

Claims 1-8, 13-21, 24-26, and 28 are drawn to methods of preparing a vaccine for treatment of subjects with cancer, methods for treating cancer with the vaccine, and drawn to compositions comprising the vaccine preparation. The methods comprise using bispecific antibodies of various types of combination isotypes.

The specification provides little guidance concerning how to use the various bispecific antibodies having any of the combination isotypes as recited in claim 1. The working example provided does not indicate whether the exemplified bispecific antibody has a combination isotype, and if it does have a combination isotype, what the combination is.

The state of the art with regard to bispecifi antibody isotype combinations is that only the rat/mouse isotype combination appears to be known (Lindhofer et al, supra). The use of combination isotypes bispecific antibodies does not appear to be well established in the art. The art of making combination isotype bispecific antibodies also appears to be unpredictable with regard to quadroma technology, and while there is an example of successful isolation of rat/mouse combinations, Lindhofer (J. Immunology, 155: 219-225, 1995) teaches that human IgG1/human IgG3 quadromas do not provide a high yield of usable bispecific antibody (see page 224, 2nd column).

As the specification provides little guidance on how to make a representative number of usable isotype combination isotype bispecific antibodies, and because the art provides very little

teachings concerning the utility of bispecific antibodies having a combination isotype, and whether such bispecific antibodies bind and crosslink Fc receptors, and because the art of making combination isotype bispecific antibodies is unpredictable, it is not clear that one of skill in the art would be able to practice the claimed inventions without engaging in undue experimentation to make and use the bispecific antibodies having isotype combinations as recited in claim 1 in the claimed methods.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

Anne L. Holleran
Patent Examiner
November 4, 2001

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